

Review Article

Faecalibacterium prausnitzii: A Next-Generation Probiotic in Gut Disease Improvement

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The researchers are paying more attention to the role of gut commensal bacteria in health development beyond the classical pathogens. It has been widely demonstrated that dysbiosis, which means the alternations of the gut microbial structure, is closely associated with development of intestinal chronic inflammation-related diseases such as inflammatory bowel disease (IBD), and even infectious diseases including bacterial and viral infection. Thus, for reshaping ecological balance, a growing body of literatures have proposed numerous strategies to modulate the structure of the gut microbiota, which provide more revelation for amelioration of these inflammation or infection-related diseases. While the ameliorative effects of traditional probiotics seem negligible, emerging next generation probiotics (NGPs) start to receive great attention as new preventive and therapeutic tools. Encouragingly, within the last decade, the intestinal symbiotic bacterium *Faecalibacterium prausnitzii* has emerged as the “sentinel of the gut,” with multifunction of anti-inflammation, gut barrier enhancement, and butyrate production. A lower abundance of *F. prausnitzii* has been shown in IBD, *Clostridium difficile* infection (CDI), and virus infection such as COVID-19. It is reported that intervention with higher richness of *F. prausnitzii* through dietary modulation, fecal microbiota transplantation, or culture strategy can protect the mice or the subjects from inflammatory diseases. Therefore, *F. prausnitzii* may have potential ability to reduce microbial translocation and inflammation, preventing occurrences of gastrointestinal comorbidities especially in COVID-19 patients.

1. Introduction

Probiotics are demonstrated to have potential anti-inflammatory and antiviral effects [1, 2]. The safety and clinical efficacy in reducing the severity and duration of upper respiratory tract infections of probiotics have been demonstrated [3]. An earlier review [4] confirmed the prophylactic and therapeutic effects of several lactic acid-producing bacteria strains on viral infection, which are reported to decrease titres of Ebola and cytomegalovirus and reduce respiratory and intestinal inflammation accordingly. Recently, Eguchi et al. evaluated the ability of *Lactobacillus gasseri* against respiratory syncytial virus (RSV) in a mice model [5]. The decreasing RSV titre and the diminishing expression of proinflammatory cytokines in the lung were significantly observed while

interferons and interferon-stimulated genes were increased after the treatment. In addition, by summarizing 15 studies of *Lactobacillus rhamnosus* GG in the treatment of acute diarrhea, Szajewska and Kołodziej [6] concluded that *Lactobacillus rhamnosus* GG could reduce the severity of purging and the duration of diarrhea by about 1 day, and the most effective dose was more than 10^{10} CFU. According to a meta-analysis, a lower dose *Lactobacillus reuteri* was also reported to be effective in reducing the duration of diarrhea by approximately 1 day [7].

Although most traditional and widely used probiotics (e.g., *Bifidobacterium* spp. and *Lactobacillus* spp.) are safe, their effect on disease improvement is uncertain. Moreover, traditional probiotics are not disease-specific. Based on these situations, there is an urgent need for identification and

characterization of novel and disease-specific next generation probiotics (NGP). As one of the most common microbial species in the colon of healthy adults, *Faecalibacterium prausnitzii* (*F. prausnitzii*) constitutes over 5 percent of the overall total bacterial population [8]. The members of the genus *Faecalibacterium* are deemed symbiotic microorganisms, omnipresent in human and animal gastrointestinal tracts (GIT) [9]. Alterations in the abundance of *F. prausnitzii* have been commonly identified to be related to a number of human intestinal and metabolic diseases [10]. Therefore, due to the pervasiveness and immunomodulator, *F. prausnitzii* is not only an important predictor but also an influential contributor to intestinal health as well as the maintenance of gut homeostasis.

Studies have shown a certain correlation between the low abundance of *F. prausnitzii* and the increased incidence of inflammatory metabolic diseases such as inflammatory bowel disease [11], Crohn's disease [12], colitis [13] and some infectious diseases such as *Clostridium difficile* infection [14], human immunodeficiency virus (HIV) [15], and hepatitis B virus (HBV) [16]. On the other hand, supplementation with *F. prausnitzii* may contribute to the amelioration of specific metabolic disorders and inflammatory diseases [17–19].

Given the above, it is fair to speculate that these anti-inflammatory and antiviral effects can well lead to the prevention and/or relief of COVID-19-related symptoms, at least partially or in combination with other medicines. Thus, this raises a possibility that *F. prausnitzii* might be a new candidate probiotic which can be used in COVID-19 patients. Herein, we discuss recent advances in the understanding of the protective effects and mechanisms on infectious diseases of *F. prausnitzii* and its potential relevance in COVID-19 infection.

2. The Bionomics of *F. prausnitzii*

F. prausnitzii is one of the most abundant and widely distributed bacterial species inhabiting the human intestine, which has been consistently described as one of the most important butyrate producers found in the intestine [20]. Taxonomically, *F. prausnitzii* belongs to the *Firmicutes* phylum, the *Clostridia* class, and the *Ruminococcaceae* family, and the species is currently the only representative characterized within the genus [9]. Metabolically, as an anaerobe, *F. prausnitzii*, a non-spore-forming and non-motile rod that is Gram-positive, is exceedingly oxygen-sensitive [9]. It is difficult to survive even in an anaerobic environment, but adding riboflavin, cysteine or glutathione to the culture medium can improve its survival rate in a microaerobic environment [21]. *F. prausnitzii* can be divided into two lineages, line I and line II, and the differences in their physiological functions are still unclear [21].

A variety of monosaccharides can be used by bacteria as their energy sources, while the use of more complex carbohydrates varies from strain to strain. The nutrients can be obtained from the host or derived from other gut microbes cross-feeding. *F. prausnitzii* can use fructose, oligofructose, starch and inulin, but not arabinose,

melibiose, raffinose, rhamnose, ribose, and xylose. Acetic acid can stimulate its growth and produce carbon dioxide, but not hydrogen [9]. The major fermentation products from glucoses and acetate by *F. prausnitzii* are formate, D-lactate, and butyrate [9].

The proportion of *F. prausnitzii* in gut microbiota is flexible affected by the colon physiological environment such as the pH, oxygen concentration, and cholate [21, 22]. Moreover, both improper diet and smoking will lead to a decreased count of *F. prausnitzii* [23]. In addition, the use of certain drugs can also modulate the abundance of *F. prausnitzii* in the intestine. For example, taking rifaximin can increase the level of *F. prausnitzii* [24], while the bacterium in the stool of Crohn's disease patients is reduced by taking infliximab and high doses of cortisol [25]. Studies have reported that butyrate produced by *F. prausnitzii* has a significant protective effect on enteritis [25]. As butyrate-producing bacteria, *F. prausnitzii* acts on the immune system and has anti-cancer effects [26, 27]. It can also improve the intestinal barrier, insulin sensitivity, and oxidative stress tolerance and reduce visceral sensitivity [28, 29].

Moreover, as one of the most abundant gut commensal bacteria, *F. prausnitzii* has the double effect of competitively inhibiting pathogenic bacteria and increasing the colonization of nonpathogenic bacteria [30], which could maintain a normal proportion of the gut microbiota. When *F. prausnitzii* is cocultured with *Bacteroides thetaiotaomicron* (*B. thetaiotaomicron*), which can also metabolize apple pectin, *F. prausnitzii* can produce more butyric acid than it alone [31]. This indicates that *F. prausnitzii* may rely on other gut microbiota including *B. thetaiotaomicron* for cross-feeding. Some studies found that the colonization of *F. prausnitzii* requires *B. thetaiotaomicron* and *Escherichia coli* (*E. coli*) to be preexisted in the intestine, which could prepare suitable conditions for *F. prausnitzii* by reducing redox potential and altering the composition of nutrients [32, 33]. In addition, *F. prausnitzii* and normal intestinal microecology can effectively prevent the proliferation of intestinal pathogenic bacteria such as *Escherichia coli*, *Clostridium*, and *Shigella*, which reduce the possibility of intestinal epithelium injury, thereby avoiding the activation of intestinal immune cells and the release of inflammatory factors [34].

Therefore, *F. prausnitzii* is a probiotic with an important protective effect on the human intestine and its reduction will lead to weakened intestinal anti-inflammatory and immune regulation capabilities.

Some characteristics of *F. prausnitzii* such as the absence of adhesion of epithelial cells [35], plasmids, antimicrobial [19, 36] and hemolytic activity, and the presence of DNase activity [19] have been known to date. In addition, only the reference strain *F. prausnitzii* A2-165 [37] and the biofilm forming strain HTF-F [38] have been examined in vitro and in vivo for their beneficial anti-inflammatory effects. Some evidence points to this symbiotic intestinal bacterium, associated with intestinal barrier integrity and inflammation regulation, as an emerging "gatekeeper of the gut."

3. Multiskilled Commensal Bacterium

F. prausnitzii

As a major member of the human microbiome, *F. prausnitzii* is a multiskilled commensal organism. It is distributed widely in the mammalian digestive tract. This bacterium has a variety of biological functions, such as regulating the immune response, suppressing inflammation, and promoting the integrity of the intestinal barrier.

3.1. Anti-inflammatory Effects. *F. prausnitzii* is a commensal bacterium with anti-inflammatory property, as demonstrated in a clinical trial [32]. Various studies have demonstrated decreasing abundance of *F. prausnitzii* in the gut could reduce protection against inflammatory interactions. This defensive mechanism possibly involves stimulating active molecules to secrete anti-inflammatory while inhibiting the secretion of proinflammatory cytokines. *F. prausnitzii* secretes anti-inflammatory molecules which can block the IL-1 β -induced NF- κ B signaling pathway, thereby reducing the production of interleukin IL-8 secreted by intestinal epithelial cells [39]. Additionally, *F. prausnitzii* can promote the secretion of IL-10 through peripheral blood monocytes, dendritic cells (DCs), and macrophages [37, 40] and consequently inhibit the synthesis of proinflammatory cytokines such as IFN- γ , TNF- α , IL-6, and IL-12 [41]. Through these mechanisms, the anti-inflammatory effect of *F. prausnitzii* in colitis may be realized, and through its anti-inflammatory properties, this bacterium may promote intestinal immune homeostasis.

3.2. Enhancement of Gut Barrier Function. Another key to intestinal development and maturity is the establishment of the integrity of the intestinal mucosa, which is not only essential for the absorption of nutrients, but also necessary for preventing bacteria and food antigens from entering the underlying tissues [42]. The metabolites released by *F. prausnitzii* have been shown to reduce the severity of inflammation by improving the function of the intestinal barrier and affecting paracellular permeability [43, 44]. Rossi et al. reported that the cell-free supernatant of *F. prausnitzii* can enhance the intestinal mucus barrier function by affecting the permeability of epithelial cells [40]. The improvement in permeability of *F. prausnitzii* appears to be related to the expression of certain tightly bound proteins [43]. It was investigated that *F. prausnitzii* could increase the levels of tight junction proteins occludin and E-cadherin and decrease colonic permeability, alleviating inflammation both in vitro and in vivo [45]. Moreover, *F. prausnitzii* may also help to maintain sufficient proportions of various cell types of secretory lineage in the intestinal epithelium via the mucus pathway and O-glycan mucus formation [31].

3.3. Effects of Metabolites. Although we have confirmed the anti-inflammatory property of *F. prausnitzii* and its supernatant, the exact active substance and its mechanism have not been fully elucidated due to its complex

composition. As an acetate consumer, *F. prausnitzii* has capacity to generate anti-inflammatory molecules such as butyrate and salicylic acids [32]. A growing body of the literature has reported that the main metabolites of *F. prausnitzii*, butyrate, play an important role in its anti-inflammatory activity. Butyrate is a short-chain fatty acid (SCFA) produced by intestinal microorganisms fermenting dietary fiber [46]. Moreover, *F. prausnitzii* has been consistently regarded as one of the main butyrate producers found in the intestine [47]. Butyrate provides energy (5–15% of the total calories) to the host and regulates the immune system, thereby protecting the host from pathogens [48].

Butyrate is secreted by intestinal microbiota and plays a significant role in intestinal physiology and body function. It is of great importance to prevent the invasion of pathogens, regulate the immune system, and reduce cancer progression [49]. As a representative of numerous pathways for electron disposal in the gut microbiota, *F. prausnitzii* can form butyrate, and its concomitant generation of NAD⁺ and decreased ferredoxin is able to facilitate immune response modulation.

Salicylic acid is another metabolic product with anti-inflammatory effects delivered by *F. prausnitzii* [32]. As strong modulators of the inflammatory process, salicylic acid can also block the activation of NF- κ B to inhibit the production of IL-8 as same as butyrate [50]. In the pharmaceutical industry, it is commonly recognized that salicylic acid can work as the forerunner of 5-aminosalicylic acid (5-ASA), which is a drug prescribed in the management procedure of IBD [24]. It has been documented in vitro that 10 mM of salicylic acid could reduce the level of IL-8 as well as the concentration found in the colon [32].

In addition, *F. prausnitzii* is capable of secreting anti-inflammatory substances including butyrate and salicylic acid, as previously described. Quévrain et al. reported another anti-inflammatory compound producing by *F. prausnitzii* called microbial anti-inflammatory molecule (MAM), which can inhibit the trigger of NF- κ B in vitro and vivo as well [18, 34]. Since MAM operates actively at the center of signaling molecule I κ B kinase α (IKK α), extra management of signal transduction molecules upstream or downstream of IKK α may significantly enhance its effects. In general, MAM could reach all over the body, and it can play a significant role in the regulation of inflammatory complications at anatomical locations outside of the intestine. The main mechanisms of *F. prausnitzii* are shown in Figure 1.

4. The Diseases Related to *F. prausnitzii*

As an important part of healthy human gut commensals, *F. prausnitzii* exerts significant actions on human health. Accumulating studies showed that the dysbiosis caused by the change of the count of *F. prausnitzii* in the intestine was closely related to the onset of some intestinal diseases such as IBD, irritable bowel syndrome (IBS), and colorectal cancer (CRC) [37, 51, 52].

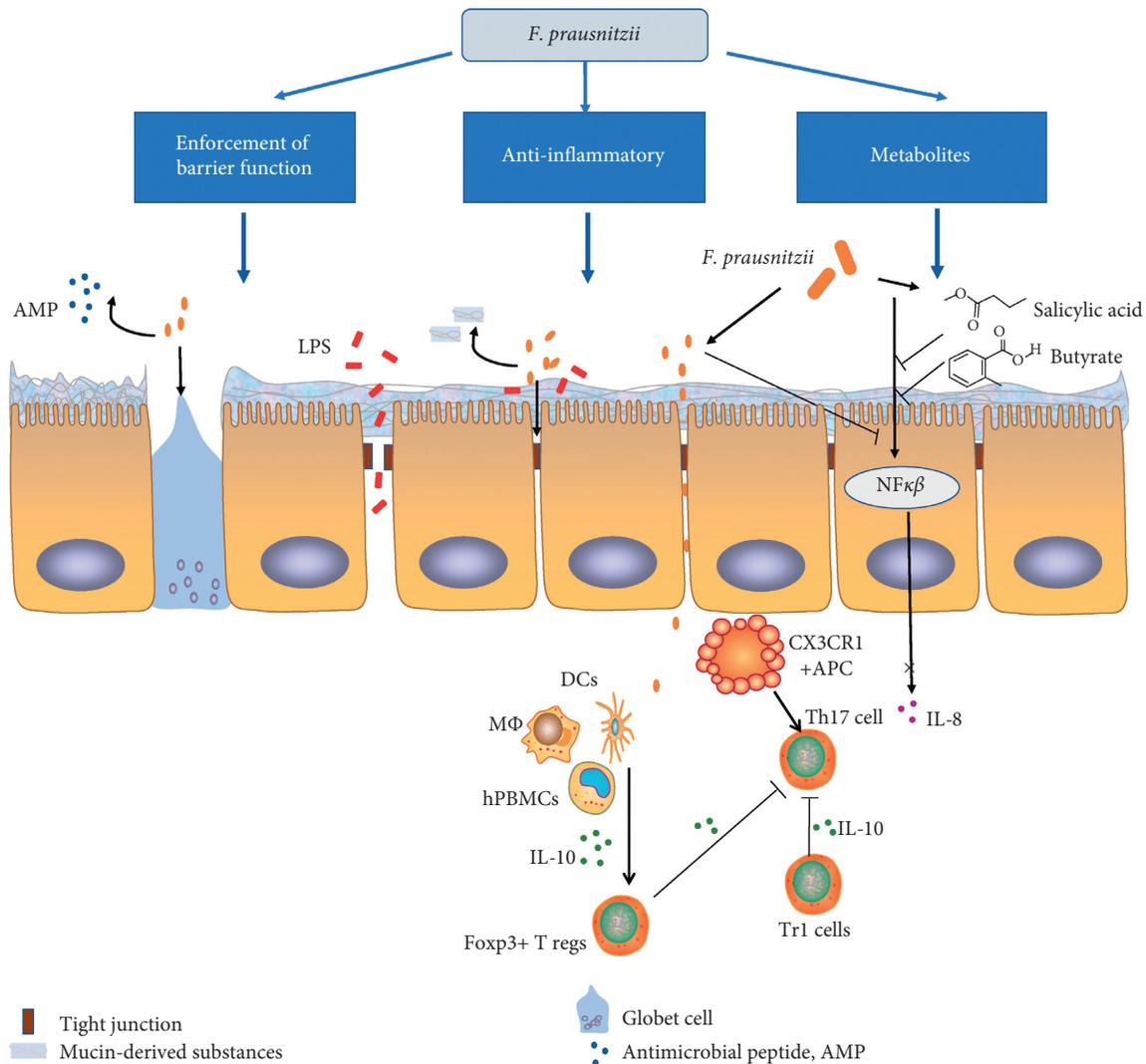


FIGURE 1: Mechanism underlying the anti-inflammation and enhancement of barrier function of *Faecalibacterium prausnitzii*. The effector molecules of *F. prausnitzii* encourage secretion of IL-10 from peripheral blood mononuclear cells (PBMCs), dendritic cells (DCs), and macrophages, and thus, proinflammatory cytokines are downregulated. The metabolites from *F. prausnitzii*, butyrate and salicylic acid, can block the secretion of IL-8 through inhibition of activation NF- κ B signaling and inflammation. The metabolites and effector molecules of *F. prausnitzii* can enhance the barrier function through providing growth factors from mucin degradation. *F. prausnitzii* could interact with the host by strengthening the intestinal barrier or modulating mucin turnover and immune responses.

4.1. IBD. Inflammatory bowel disease (IBD), whose two major forms are ulcerative colitis (UC) and Crohn's disease (CD) [53], is a chronic inflammation of the intestine induced by immune response under environmental conditions such as genetic susceptibility, diet, and antibiotic use. In the past few decades, plenty of clinical research data has shown that the composition and diversity of microbiota is modified in patients with IBD. Compared to that in healthy people, an increasing abundance of *Proteobacteria* was observed in the fecal microbiota of patients with active CD and UC, while lower fecal counts of *Firmicutes* were detected [37]. *F. prausnitzii*, as the most abundant bacteria in human

intestine, possesses a small amount in CD and UC patients [54]. Machiels et al. found that there was a significant inverse association between the count of *F. prausnitzii* and disease activity in UC patients, even with the inactive disease [55]. Moreover, regarding the metabolites, decreasing short-chain fatty acids were observed in patients with UC [55]. Recently, Zhao et al. performed a systematic review and meta-analysis involving patients with UC and CD [56]. They found that both CD and UC patients had a lower abundance of *F. prausnitzii* than the healthy controls and a lower count of *F. prausnitzii* was detected in patients with active IBD in contrast with those in remission. In addition, it was reported

that patients receiving infliximab, a TNF- α blocker, showed an increase in *F. prausnitzii* population [57], which suggested a relationship in the pathomechanisms of IBD.

4.2. CDI. In addition to gut diseases, recent studies have shown the potential relevance between *F. prausnitzii* and infectious diseases such as CDI, HIV, and HBV. This will undoubtedly be a hotspot on *F. prausnitzii* worth studying in the future.

A study reported that patients with CDI had significantly fewer members of *F. prausnitzii* in their fecal microbiota than the healthy group [58]. Demirci et al. found that the amount of *F. prausnitzii* was reduced in patients with allergic diseases, which might suppress inflammation by decreasing proinflammatory cytokines such as IL-12 and increasing anti-inflammatory cytokine IL-10 [59]. Roychowdhury et al. revealed that supplementation with anti-inflammatory butyrate-producing commensal bacteria and prebiotic might help to promote innate immune responses and minimize bacterial burden and adverse effects during a course of antibiotic and *Clostridium difficile* exposure [60]. Moreover, a study observed increased *F. prausnitzii* in a cured recurrent CDI patient who had received fecal microbiota transplantation (FMT) 4.5 years ago.

Le Bastard et al. [61] discovered that ampicillin resulted in a sharp drop in bacterial species richness and diversity along with a fall in the percentage of *F. prausnitzii*. In mice receiving FMT, dysbiosis was immediately reversed with a significant increase in *F. prausnitzii*.

4.3. Virus-Infected Gut Dysfunction. Furthermore, Lu et al. found that gastrointestinal microbiota changes were linked to CD4⁺ T-cell counts and immune activation in those with HIV [14]. In that study, *F. prausnitzii* is overrepresented in HIV-infected individuals who are immunological ART nonresponders or untreated compared to those immunological ART responders. Similarly, another study revealed that *F. prausnitzii* was depleted in HIV-positive persons on long-term ART compared to HIV-negative and the amount of *F. prausnitzii* has a negative correlation with gut dysfunction [15]. It has also been observed that the count of *F. prausnitzii* in asymptomatic carriers showed significant variation, and the variation range was considerably higher in patients with chronic hepatitis B and those with decompensated HBV cirrhosis in comparison with healthy controls [16]. These findings have revealed the potential connection between *F. prausnitzii* and viral infectious diseases, suggesting the possibility of *F. prausnitzii* as a targeted probiotic in the treatment of viral infectious diseases.

5. Strategies to Modulate the Abundance of *F. prausnitzii*

Due to the fact that all the *F. prausnitzii* strains from feces of healthy individuals showed positive anti-inflammation [62], it could be a promising target for therapeutic purpose. However, the production of medical supplements using obligate anaerobes, such as *F. prausnitzii*, is certainly a major

challenge owing to the requirements for anaerobic conditions and mass production. Herein, we propose strategies to increase the abundance of *F. prausnitzii* from three perspectives.

5.1. Dietary Interventions Modulate *F. prausnitzii*. The structure of microbial communities of human beings depends, to a great extent, on the dietary factor, for bacterial composition in the gut is closely related to the available nutritional compounds [62]. The intake of the typical westernized diet which means a large amount of animal meat, sugar, animal fat, processed foods, and low fiber diet could reduce *F. prausnitzii*, whereas a high fiber diet with less meat can increase *F. prausnitzii* [63]. Hence, the abundance of *F. prausnitzii* can be regulated through the consumption of prebiotics and/or formulations. Treatment with inulin-type fructans and fructo-oligosaccharides has been demonstrated to increase the level of *F. prausnitzii* compared to placebo (maltodextrin) in patients [64]. Supplementation of prebiotic inulin-oligofructose also led to an increase of *F. prausnitzii* in healthy individuals [65]. An increase of *F. prausnitzii* was reported for red wine intake compared to baseline in male metabolic syndrome patients and healthy individuals [66]. Another study found that healthy men who consumed polydextrose or soluble corn fiber supplements had more *F. prausnitzii* than men who did not take fiber supplements, suggesting that this might be potential prebiotics [67]. In a research on the effects of a low-energy diet with prebiotic properties for patients with type 2 diabetes, *F. prausnitzii* increased by 34% compared to a placebo diet [68].

F. prausnitzii is reported to consume various diet including polysaccharides, such as the prebiotic inulin, arabinoxylans, resistant starch, fructan supplement, and ectins [63, 69]. As the most important modulators of gut microbiota, polysaccharides are generally consumed in the food because of their relative security, availability, and low price. A study demonstrated that increased consumption of polysaccharides had the potential to give advantage to individuals with a typical western-style diet, on condition that they take in enough dietary fiber [70]. As shown in several meta-analyses, the increased intake of dietary fiber greatly reduces the mortality risk [71].

5.2. Fecal Microbiota Transplantation. In recent years, there has been considerable interest in FMT, which is implemented by transferring the microbiota from healthy donors to people suffering from dysbiosis to restore eubiotic state. In an earlier study, van Nood et al. demonstrated that FMT could heal recurrent CDI, targeting the gut microbiota which can exert profound influence on the host metabolism [72]. Furthermore, researchers found that infusion of donor feces was significantly more effective for the treatment of recurrent CDI than the use of antibiotics. Moreover, in order to treat Crohn's disease and ulcerative colitis, Cui et al. proposed a step-up FMT strategy consisting of a FMT, then by further FMT steps or standard IBD prescriptions depending upon the patient's therapeutic response [73]. It is known that FMT can influence the growth of

Bacteroidetes and *Firmicutes*, especially *F. prausnitzii* [74]. A recent study investigates the safety and effectiveness of FMT in patients with mild or moderate UC by giving 47 patients treatments of fresh FMT. It shows that FMT resulted in clinical remission in patients with mild to moderate UC and that the remission may be associated with significantly increased levels of *F. prausnitzii* [75]. Sarrabayrouse et al. investigate changes in recipient intestinal mucosa upon contact with a fecal suspension (FS) obtained from a healthy donor by using a human explant tissue model and an in vivo mouse model. Interestingly, it shows that tissues with a low microbial load and a higher relative abundance of *Firmicutes* were more susceptible to FMT [76]. These studies suggest that *F. prausnitzii* can be a diagnostic and therapeutic candidate for the use of FMT in UC.

However, beneficial effects of FMT can be affected by dietary and host immune factors. The microbial structure of a healthy individual must be taken into account in time and in accordance with dietary, immune, and aging influences. In addition, the potential risk of the transmission of obesity and metabolic syndrome associated flora ought not to be ignored. FMT from the obese ones caused an increase in adiposity in mice, indicating the potential risk of transmission of some diseases associated flora [77]. Therefore, FMT needs further assessment.

5.3. Cultivate *F. prausnitzii* In Vitro. In addition to fecal microbiota transplantation and dietary regulation, how to cultivate *F. prausnitzii* in vitro is of vital importance. At present, the research on the isolation of *F. prausnitzii* and the exploration of the relationship between *F. prausnitzii* and diseases from the strain level are still in the preliminary stage at home and abroad. Therefore, the isolation and identification of *F. prausnitzii* and the screening of excellent strains that are correlated with human health and have strong biological activity have become an important prerequisite for further in-depth research on it. *F. prausnitzii* is extremely oxygen-sensitive, which may lose validity when exposed to the air for 2 minutes, and it is difficult to cultivate even in an anaerobic environment [9]. Adding riboflavin and cysteine or glutathione to the medium can make it grow in low oxygen environment [78]. In order to adapt to the micro-oxygen environment in the intestine, *F. prausnitzii* uses flavin and thiols as shuttle carriers inside and outside the cell to transfer electrons to oxygen and protect itself from oxidative stress [78]. Khan et al. found that the obligate anaerobic *F. prausnitzii* can be kept alive at ambient air for 24 h in a growth medium formulated with the antioxidants cysteine and riboflavin plus the cryoprotectant inulin [79]. It suggests that we can improve the growth of *F. prausnitzii* in vitro by changing the composition of the medium.

6. Potential Clinical Applications of *F. prausnitzii* in Diseases, Even in COVID-19 Infection

Since *F. prausnitzii* is extremely sensitive to changes in the intestinal environment, fecal- or mucosal-related *F. prausnitzii* can be regarded as a potential biomarker for diagnosis of

intestinal diseases. However, a single bacterial species cannot be a universal biomarker for all types of diseases. Lopez-Siles proposed that the F-E index obtained by combining the abundance of *F. prausnitzii* and *E. coli* can be a better indicator than the single specie [80], which could discriminate between CD, IBS, and CRC [25, 52, 80], also distinguish CRC patients from other intestinal diseases. Since IBD is a chronic disease, many researchers paid their attention to the use of biomarkers to predict its prognosis. The lower CD activity index, C-reactive protein levels, and erythrocyte sedimentation rate have been demonstrated to be related to higher *F. prausnitzii* counts in feces [12]. Furthermore, disease remission could recover the abundance of *F. prausnitzii* in feces [13, 25]. However, the current research studies on the characteristics and functions of this bacteria are not enough intensive and extensive. There is a need for more in-depth study on the functional activity of *F. prausnitzii* and its potential as a biomarker.

In addition, as a treatment strategy, transplantation of *F. prausnitzii* has been widely used in dysbiosis of the intestinal flora that is associated with the inflammation, autoimmune disease, and infectious diseases. Butyrate-producing bacteria have been demonstrated to prevent translocation of endotoxin, which is a compound produced by the gut microbiota and has been reported to drive insulin resistance [81]. Sokol et al. [13] designed an in vitro experiment to prove that human immune cells with *F. prausnitzii* can show a potential anti-inflammatory response in the gut. At the same time, they revealed that the transplantation of *F. prausnitzii* in mice could shield the gut epithelium from destruction and inhibit gut inflammation induced by experimental reagents. Additionally, several research studies have demonstrated that oral *F. prausnitzii* has an anti-inflammatory effect in IBD mice models [82, 83]. Overall, transplantation of gut microbiota particularly *F. prausnitzii* from a healthy individual to subjects with metabolic syndrome or intestinal inflammation could modulate dysbiosis and inhibit downstream proinflammatory response.

Furthermore, respiratory viral infections have been reported to be associated with altered gut microbial structure, which predispose patients to secondary bacterial infections [84]. Probiotics may be an effective adjuvant strategy for the treatment and prophylaxis of viral infections including COVID-19. Numerous experts and scholars have proposed the use of probiotics to participate in the treatment of COVID-19 [85, 86], so it is important to screen out new probiotics. Moreover, according to a recent science blog by the IASPP (International Scientific Association for Probiotics and Prebiotics), numerous researchers around the world are studying the susceptibility of the microbiome to COVID-19 and assessing the ability of various probiotic strains to reduce viral load through multiple mechanisms of action.

Researchers performed transcriptome sequencing on the bronchoalveolar lavage fluid of COVID-19 patients, and the results showed that the microbiota was dominated by pathogens or oral and upper respiratory commensal bacteria [87]. Furthermore, it has been demonstrated comorbidities generally associated with severe COVID-19 are closely related to alterations in bacteria taxa from the phyla *Bacteroidetes* and *Firmicutes* [88, 89], which were reported to regulate ACE2 expression in rodents.

To the best of our knowledge, ACE2 is known as the receptor for SARS-CoV-2 to enter the host, which is highly expressed in both the respiratory and gastrointestinal tract [90]. In addition, it plays a role in controlling intestinal inflammation and maintaining intestinal microbial ecology [91]. Interestingly, *Firmicutes* species seemed to have diverse roles in regulating ACE2 expression in the colon of mice models [92]. Moreover, Zuo et al. found that there was an inverse correlation between abundance of *F. prausnitzii* and COVID-19 severity [93]. In this study, *F. prausnitzii* was discovered to be one of the top bacterial species which show a negative correlation with COVID-19 severity.

Clinical data showed that older patients and those with underlying chronic diseases related to inflammation (such as hypertension, obesity, diabetes, and coronary artery disease) had higher SARS-CoV-2 mortality and morbidity [94, 95]. Interestingly, the abundance of *F. prausnitzii* was reported to be lower in these subjects compared with healthy individuals [96–98]. Hence, it seems reasonable that *F. prausnitzii* can be an add-on therapy for the management of COVID-19.

The possible role of *F. prausnitzii* abundance in COVID-19 infection in terms of gut integrity and inflammation needs to be further elucidated. Its potential prognostic and therapeutic value in SARS-CoV-2 infections is waiting to be explored.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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